JAMA Insights

Management of Severe Refractory Asthma

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Asthma, the most common chronic airway disease worldwide, is associated with substantial morbidity and mortality, with 3624 deaths annually in the US[1] and approximately 365 000 deaths annually worldwide.[2] Severe refractory asthma affects approximately 1% to 5% of patients with asthma and is defined as disease that remains uncontrolled despite treatment with high-dose inhaled corticosteroids (ICS) plus 1 or more additional controller therapies (eg, long-acting β-agonists) in patients who are adherent to therapy, use correct inhaler technique, and receive treatment for comorbidities that may exacerbate asthma (eg, allergic rhinitis, chronic rhinosinusitis, and gastroesophageal reflux disease).[3] Patients with severe refractory asthma may experience accelerated loss of lung function[4] and have increased mortality rates associated with exacerbations than individuals with more mild forms of asthma.[5]

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Most patients in the US with severe refractory asthma are exclusively treated by primary care clinicians.[6] A 2024 observational, retrospective analysis of 2 large claims databases reported that only 50.4% of patients (45 545 of 90 368) with uncontrolled asthma (defined as recurrent visits to the emergency department or hospital for asthma) visited an asthma specialist in the year following an asthma exacerbation, regardless of medical insurance type.[7]

Type 2 (T2)–high asthma, the most common subtype of severe refractory asthma among both children and adults, is characterized by high levels of T helper 2 inflammatory cytokines, such as interleukins 4, 5, and 13, and elevated eosinophils and fractional exhaled nitric oxide. T2-high asthma, which is associated with a higher risk of exacerbation compared with T2-low asthma, is more responsive to biologic therapies, which primarily target T2-driven inflammation. However, biologics are inaccessible to many eligible patients due to limited access to asthma specialists, who prescribe more than 90% of biologic prescriptions.[8]

Evaluation of Patients With Severe Refractory Asthma

All patients with severe refractory asthma should undergo pulmonary function testing with prebronchodilator and postbronchodilator testing, complete blood cell count with differential (to determine blood eosinophils), total serum IgE, fractional exhaled nitric oxide (available at many asthma clinics and some primary care practices and hospitals), and environmental allergy testing (eg, pollen, pet dander, dust mites, mold) with skin prick testing or allergen-specific blood IgE testing. Pulmonary function tests assess for airflow obstruction and bronchodilator responsiveness and are used to monitor lung function, which can decline with frequent asthma exacerbations due to airway remodeling. Total IgE and environmental allergen testing help identify allergic asthma, can guide exposure reduction strategies, and determine eligibility for anti-IgE therapy (omalizumab). Testing should be interpreted by allergists, as pretest probability significantly affects diagnostic accuracy (ie, the positive predictive value of allergy tests alone may be as low as 50% but improves substantially when supported by clinical history).[9]

Nonpharmacologic Management

All allergen-sensitized patients with asthma should reduce indoor exposures (eg, dust mites, mold, pests) by using dust mite encasements for mattresses and pillows, washing bedding weekly in hot water, and vacuuming with high-efficiency particulate air filters. If present, pest and mold remediation are also recommended. Allergen-specific immunotherapy can be beneficial but should not be initiated until asthma is controlled and forced expiratory volume in the first second of expiration (FEV_1) exceeds 70% predicted.[2] During peak allergy season, patients with asthma and seasonal allergies should keep windows closed and bathe before bed to remove pollen from their skin and hair. Patients with asthma should also be informed about nonallergenic triggers, such as tobacco smoke, vaping, cannabis, biomass fuels (eg, wood-burning stoves), and air pollution, which exacerbate airway inflammation. Avoiding or reducing these exposures can substantially improve asthma control.[2,10]

Medications for Severe Refractory Asthma

First-line treatment for all patients with severe refractory asthma includes daily ICS, often in combination with a long-acting β-agonist and a long-acting muscarinic antagonist to target persistent airway inflammation and improve symptom control. Inhaler technique should be assessed for all patients with severe refractory asthma to ensure that the inhaled medication is being administered correctly. For patients who have difficulty with proper inhaler technique, changing delivery device types (eg, switching from a dry powder to a metered-dose inhaler) or using a spacer may improve medication delivery. Anti-inflammatory reliever strategies, which allow patients to escalate ICS therapy, along with a fast-acting bronchodilator (albuterol or formoterol) in response to worsening symptoms, have been shown to significantly reduce asthma exacerbations. For example, the PREPARE study demonstrated that a patient-activated, reliever-triggered ICS strategy led to a 15% reduction in severe exacerbations and a 3.4-point improvement in Asthma Control Test scores (minimum clinically important difference, 3 points) among 1201 Black and Latinx adults with moderate to severe asthma.

Patients with moderate to severe asthma whose asthma remains uncontrolled despite treatment with ICS plus a second controller, those with frequent asthma exacerbations, and those who require maintenance oral corticosteroids should be referred to an asthma specialist for evaluation for biologic therapy. Currently, 6 biologics are approved by the US Food and Drug Administration for moderate to severe asthma in children and adults (**Table**). Although direct comparisons of biologic efficacy are limited by heterogeneity of study design and absence of comparison trials, treatment with biologics has been associated with a 44% reduction in the annualized rate of asthma exacerbations (rate ratio, 0.56 [95% CI, 0.51-

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Table. Biologics for the Treatment of Severe Refractory Asthma

	Omalizumab[a]	Mepolizumab	Benralizumab	Reslizumab	Dupilumab	Tezepelumab
Target	IgE	IL-5	IL-5Rα	IL-5	IL-4Rα	TSLP
Mechanism of action	Prevents circulating IgE binding to high-affinity IgE receptor on mast cells and basophils, reducing degranulation	Binds to IL-5 and prevents binding to IL-5Rα on eosinophils	Binds to IL-5Rα on eosinophils and basophils, marking for cell-mediated cytotoxicity	Binds to IL-5 and prevents binding to IL-5Rα on eosinophils	Binds to receptor subunit shared by IL-4 and -13, blocking upstream signaling in type 2 cascade	Prevents TSLP binding to TSLP receptor on dendritic cells, mast cells, type 2 innate lymphoid cells, and T helper 2 cells
Administration route, dosing interval, and age[b]	SC every 2 or 4 wk, ≥6 y[c]	SC every 4 wk, ≥6 y	SC every 8 wk, ≥6 y[d]	Intravenous every 4 wk, ≥18 y	SC every 2 or 4 wk, ≥6 y[e]	SC every 4 wk, ≥12 y
Key biomarker eligibility criteria	Sensitization to a perennial aeroallergen and pretreatment total serum IgE	Peripheral blood AEC ≥150/μL	Peripheral blood AEC ≥150/μL	Peripheral blood AEC ≥400/μL	Peripheral blood AEC ≥150/μL	Effective across broad range of peripheral blood AECs, but higher AEC counts predict better responses
Potential adverse effects	Anaphylaxis occurs in ~0.2% of patients; SSLRs and EGPA reported	Herpes zoster reactivation; case reports of anaphylaxis	Case reports of anaphylaxis	Anaphylaxis occurs in 0.3% of patients	Transient blood eosinophilia, EGPA, and eosinophilic pneumonia; live vaccines should be avoided	Live vaccines should be avoided

Abbreviations: AEC, absolute eosinophil count; EGPA, eosinophilic granulomatosis with polyangiitis; SC, subcutaneous; SSLR, serum sickness-like reaction; TSLP, thymic stromal lymphopoietin.

[a] A generic biosimilar is now available for omalizumab, although its impact on out-of-pocket costs remains to be determined.

[b] Age applied to the asthma indication only.

[c] Dosing frequency of every 2 to 4 weeks was determined by weight and pretreatment total serum IgE levels.

[d] Every 4 weeks for the first 3 doses, then every 8 weeks.

[e] Dosing frequency of every 2 to 4 weeks was determined by age and weight.

0.62]) and a 60% decrease in hospitalizations (rate ratio, 0.40 [95% CI, 0.27-0.60]), highlighting their substantial effect on clinical outcomes. Improvements in lung function and symptom control with use of biologics are generally more modest, with a mean increase in FEV_1 of 0.11 L and a decrease in Asthma Control Questionnaire score of 0.34 points (minimum clinically important difference, 0.5). Omalizumab, mepolizumab, benralizumab, and dupilumab are approved for home administration, enhancing convenience of administration. All asthma biologics cost $30 000 per year or more, with prices varying with dose and frequency of administration.

Conclusions

Patients with severe refractory asthma benefit from management of comorbidities and environmental triggers and access to asthma specialists to optimize medications, including prescription of biologics.

ARTICLE INFORMATION

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